Paper PP04

Introduction to the ADNCA ADaM

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ABSTRACT

Pharmacokinetics (PK) is an integral part of drug development as it is the process of analyzing the movement of drugs within the body. In order to describe, characterize, and quantify this effect, PK parameters are required to be calculated. This poster will provide an overview of the ADNCA (Data for Non-Compartmental Analysis) ADaM Dataset and how it is an effective way of generating a dataset that will contain the required data for calculating the PK Parameters. It will compare the ADNCA method to older processes used to aid PK Parameter derivation, and how it will improve efficiency during a study.

INTRODUCTION

Non-compartmental PK analysis provides information about drug exposure and its interactions within a participant's body throughout a study. This can include but is not limited to algebraic equations to calculate parameters such as maximum concentration (Cmax), area under the concentration-time curve (AUC), elimination like half-life (t1/2), and clearance.

To calculate the necessary PK parameters, the raw PK data needs to be processed and provided in a programmed dataset containing key details such as participant dosing information and study specific derivation flags. While existing PK input dataset methods can vary in process, the use of the standardized ADNCA ADaM dataset creates a useful dataset in an efficient manner. The utilization of ADNCA can be beneficial at multiple points throughout a study since it can replace both the PK input dataset and ADPC ADaM, meaning it can be used directly to produce the concentration TFLs.

OVERVIEW OF KEY VARIABLES

The ADNCA dataset follows the Basic Data Structure (BDS) as described in the ADaM Implementation Guide (IG). This means that the standard expected variables found in standard BDS ADaM datasets are also required in the ADNCA, including those provided by the ADSL.

ADSL VARIABLES

In addition to study ID and subject number identifiers, ADNCA retains any information that is required in the PK analysis from ADSL.

COMPFL	Completers Population Flag.
AGE/AGEU	Age/Age Units
RACE	Race
ETHNIC	Ethnicity
SEX	Sex

BDS CORE VARIABLES

The standard BDS variables are explained in ADaM IG 1.3 however below lists the types of variables that are expected in ADNCA.

PARAM/PARAMN	Parameter/Parameter (N)
PARAMCD	Parameter Code
AVISIT/AVISITN	Analysis Visit/Analysis Visit (N)
ATPT/ATPTN	Analysis Timepoint/Analysis Timepoint (N)
ADT/ATM	Analysis Date/Analysis Time
AVAL/AVALU	Analysis Value/Analysis Value Unit
DTYPE	Derivation Type
TRTP/TRTA	Planned Treatment/Actual Treatment

Variables such as PARAM, AVISIT and ATPT should be populated in the format that is required as per the TFL shells.

REQUIRED VARIABLES

The ADNCA dataset follows its own IG – Analysis Data Model Implementation Guide for Non-compartmental Analysis Input Data – which means it contains additional required variables in comparison to a standard BDS ADaM. The variable AVISIT listed in the above section is also a required variable in ADNCA.

DOSEA	Actual Treatment Dose; *This variable contains the actual treatment dosage.*
DOSEU	Treatment Dose Units; *Contains the units for DOSEA, (and DOSEP if required on study)*
PCRFTDT	Reference Date of Dose for Analyte; *Date of reference exposure to treatment associated with PARAM. Based on PC.PCRFTDTC and related to the analyzed profile.*
PCRFTTM	Reference Time of Dose for Analyte; *Time of reference exposure to treatment associated with PARAM. Based on PC.PCRFTDTC and related to the analyzed profile*.
PCRTFDTM	Reference Datetime of Dose for Analyte; *Date and time of reference exposure to treatment associated with PARAM. Based on PC.PCRFTDTC and related to the analyzed profile.*
NRRLT	Nominal Rel. Time from Ref. Dose; *This is the planned elapsed time (for sample point or start of sampling interval) from reference exposure to study treatment.*
ARRLT	Actual Rel. Time from Ref. Dose; *This is the actual elapsed time (for sample point or start of sampling interval) from reference exposure to study treatment.*
RRLTU	Rel. Time from Ref. Dose Unit; *This is the unit for all elapsed times from reference dose.*

Before programming any ADNCA, a programmer should receive a set of instructions from the Pharmacokineticist on certain occurrences that need flagging in order for them to complete analysis. With guidance from the Pharmacokineticist, relevant analysis information such as Trailing BLQs and Positive Predose records can be identified with derived flagging variables. This is similar to the existing expectations for analysis flags in the standard set of ADaM datasets. There are Conditional and Permissible variables in the ADNCA IG that can be utilized to meet these requirements as well as variables such as MRRLT (Modified Rel. Time from Ref. Dose) which can be used to modify ARRLT based on analysis needs such as have it set to 4 decimal places.

AFTER ANALYSIS

Once the ADNCA has been sent to the Pharmacokineticist for analysis, they will send a file back which includes concentration and participant flags and exclusions which can be read directly back into ADNCA. With these, the programmer is able to assign flags within the ADNCA to determine which records or participants are excluded from descriptive statistic outputs.

COMPARISON OF PROCESS

DIFFERENCES

While a PK input data dataset would need its own specification to provide variable information, ADNCA is defined as an ADaM dataset so this information can be included in the ADaM specification file. This can aid with increasing the scope of relevant information available in the file, as well as simplifying the specification process.

The outcome of PK analysis can often result in an additional flagging file to identify specific records for a participant; these can aid the creation of the PK TFLs to flag any records which should be excluded from summary statistics and overall analysis. When using a PK input data process, these flags are presented in the SDTM supplementary datasets for PC and PP (SUPPPC and SUPPPP respectively). Since SDTM PC is typically used for the PK input data source, this can lead to inconsistent rerun dates, and results in updates needed for both the SDTM PC and the ADPC ADaM dataset. Alternatively, ADNCA can be used replace to ADPC, and the flagging file details can be included directly at the ADaM level, bypassing the need to update the SDTM PC and SUPPPC datasets.

SIMILARITIES

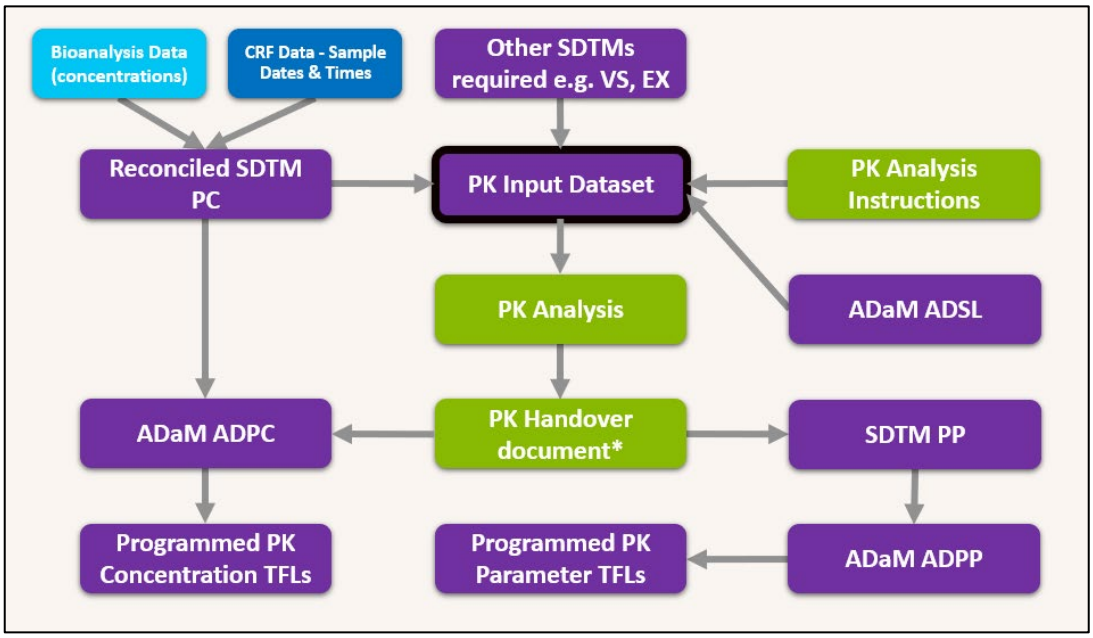
The non-compartmental PK analysis needed for a study should not change regardless of the dataset method used. Because of this, the instructions provided by the Pharmacokineticist will not alter despite the differing programming process of ADNCA. Similarly, the flagging file created from the PK analysis is not expected to vary significantly since the core meaning of the data provided and the need for flagging records for exclusion remains consistent between the two dataset types.

The intention of the ADNCA ADaM is to be able to produce the same PK TFL outputs as those created using an ADPC, without the need for an additional interim dataset to facilitate the necessary analysis. There should be no significant differences to the standard PK TFL presentation expected for the final outputs.

PROCESS FLOW

The process flow for using a PK input data method is shown in Figure 1 below.

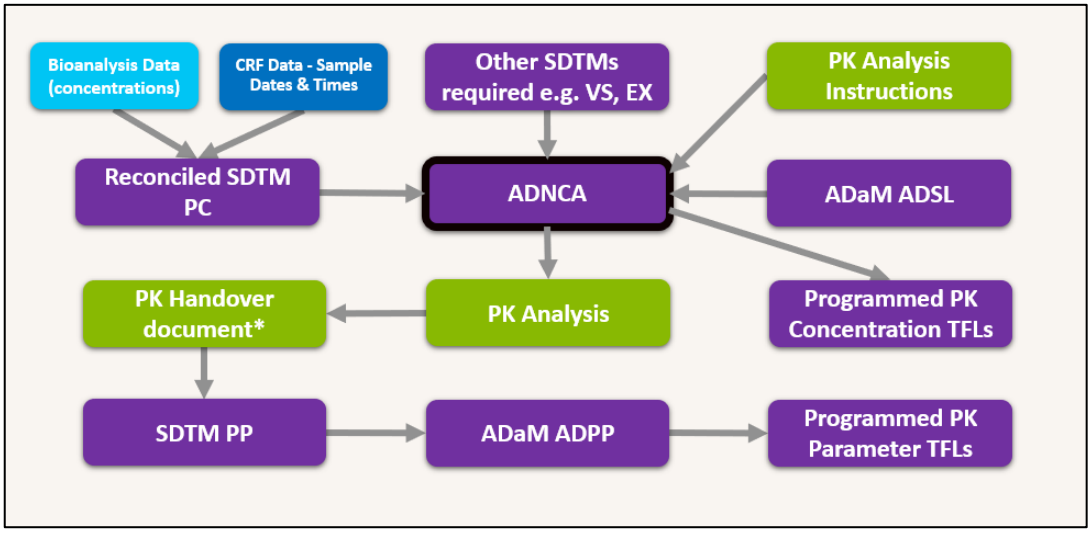
Figure 1



* Includes PK Parameters and Flagging Documents

The process flow for using the ADNCA method is shown in Figure 2 below.

Figure 2



* Includes PK Parameters and Flagging Documents

BENEFITS OF USING THE ADNCA

TRACEABILITY

A key benefit of the ADNCA process is the increased traceability. As part of the ADaM datasets for a study, it can be submitted within the ADaM Case Report Tabulation (CRT) package. This means mapping and derivation methods are accessible in the Define.xml, aiding the clear and thorough understanding of how the data is handled from the source raw PK file through to the SDTM and ADaM datasets. Additionally, it provided more opportunity for further details to be included in the Analysis Data Reviewers Guide (ADRG); including explanations of flags used for PK analysis and clarifying any possible data issues.

EFFICIENCY

With the ever-increasing demand for efficient process methods, ADNCA can aid with streamlining the statistical programming responsibilities for handling PK data. Not only is the programming reduced to a single code file, but valuable time can also be saved because the specification for the dataset can be part of the ADaM specification instead of its own file. Minimizing the necessary documentation can help reduce durations of reruns and updates if PK analysis is needed multiple times throughout a study.

CONSISTENCY

Duplicate code increases the risk of inconsistent methods. These inconsistent methods may occur when data flags are needed in both the PK input data and ADPC. Having the necessary flags in ADNCA removes this risk since the dataset can be used for the source of PK analysis and as the PK concentration ADaM dataset for a study. This means that the flags will only need to be derived once and will maintain the same information before and after analysis.

VALIDATION

Although internal quality check processes can be performed within a company for PK input datasets, the lack of standardization across the industry limits the level of review which can be performed. The clear IG available for ADNCA can help ensure the programmed output is not only consistent across studies but is also accurate to the available data. Furthermore, the standardized dataset can be validated via Pinnacle21 software, providing a more thorough quality check beyond manual review which is more at risk to human error.

CONCLUSION

Using the ADNCA dataset gives the industry an opportunity to streamline the entire PK Dataset and TFL process. Having scope to reduce PK programming timelines can be critical for many studies, especially within the fast-paced environment of Early Phase research.

This process creates a robust dataset which presents the key PK information for a study that can be thoroughly reviewed and validated. This in turn aids with the production of reliable PK analysis and subsequent TFL outputs. Validation and reviews are supported by the formalized ADNCA IG and inclusion in the Pinnacle21 checks.

REFERENCES

- Non-compartmental Pharmacokinetic Analysis
- CDISC Analysis Data Model Implementation Guide
- Analysis Data Model Implementation Guide for Non-compartmental Analysis Input Data
- Coming soon: ADNCA and the PK submission
- Unveiling the Potential of ADNCA by CDISC ADaM IG: Revolutionizing Pharmacokinetic Non-Compartmental Analysis Input Data Standardization

CONTACT INFORMATION

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